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Effect of Electron Radiation on Aggressive Behavior, Activity, and Hemopoiesis in Mice

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The behavioral and physiological effects of 10 Gray (Gy) LINAC electrons in male Swiss-Webster mice were followed for 12 days postirradiation (PR). In Experiment 1, aggressive behavior was assessed in irradiated or sham-irradiated resident mice using a resident-intruder paradigm. Aggressive offensive behavior in the irradiated residents was significantly decreased beginning 2 to 5 days PR, and remained suppressed. Defensive behavior in the nonirradiated intruders was decreased significantly by day 5 PR. In Experiment 2, spontaneous locomotor activity was monitored. Ambulation of irradiated mice was significantly depressed from day 5 PR on, while rearing was affected as early as day 2 PR and remained suppressed. Body weights of irradiated animals were significantly decreased by 5 days PR. In Experiment 3, blood parameters were examined. Compared to sham-irradiated controls, leukocytes, erythrocytes, and hematocrit of irradiated mice were reduced significantly beginning on day 1 PR and remained suppressed, while platelets and hemoglobin were decreased beginning day 2 PR. These results demonstrate that 10 Gy of high-energy electrons results in earlier behavioral deficits than has been observed previously with the same dose of gamma photons.

INTRODUCTION

Exposure to electron fluxes in the Earth's radiation belt presents a serious problem for manned space flight and is of special concern for proposed missions to Mars, the establishment of lunar bases, and the use of geostationary orbits^{12,17}. Low doses of radiation can exert subtle effects on the nervous system, resulting in possible behavioral decrements that would interfere with the successful completion of a space mission^{4,15,29}. Exposure to higher doses of radiation can result in severe early performance decrements, anorexia, nausea, emesis, fever, and diarrhea. These symptoms are followed by anemia, immunosuppression, hemorrhage, and muscular weakness^{4,9,14}, all of which could present serious threats to astronauts.

Previous research has demonstrated that electron radiation may exert a greater suppressive

effect on behavior than other qualities (types) of radiation, including gamma photon, bremsstrahlung, and neutron radiation. For example, a study measuring performance on an accelerod, a shock-motivated test of motor coordination, revealed that the ED50 (median effective dose) for disruption of motor behavior for electrons, gamma photons, bremsstrahlung, and neutron radiation was 61, 89, 81, and 98 Gy, respectively^{3,5}. Similarly, the ED50 for suppressing shock-avoidance behavior on a jump task in rats was 62 Gy for electron radiation and 102 Gy for gamma photons¹⁵. Moreover, a dose of 100 Gy electrons produced the same degree of radiation-induced catalepsy in rats as 150 Gy gamma photons¹⁶, (Dr. S.B. Kandasamy, personal communication). Whole-body irradiation of rats with 10 Gy electrons produced similar perturbations in calcium channel uptake in synaptosomes as did whole-body irradiation with 20 Gy gamma photons (Dr. S.B. Kandasamy, personal communication).

While electrons may be more effective than other qualities of radiation at suppressing some types of behavior, this is not true of all behavioral measures. In miniature pigs, head-only irradiation with 88 Gy electrons produced the same degree of deficit in shock-avoidance behavior in a shuttlebox as irradiation with 88 Gy mixed gamma-neutrons^{10,11}. Development of conditioned taste aversion in rats was affected more severely by high-energy iron particles and neutrons than by electrons: a maximal radiation-induced conditioned taste aversion was produced by irradiation with 0.3 Gy high-energy iron particles, 1 Gy neutrons, 5 Gy gamma photons, or 5 Gy electrons²⁵.

In the present studies, the effects of high-energy electron radiation on aggressive behavior, locomotor activity, and body weight were assessed. Blood parameters were also monitored to determine if behavioral changes were correlated with radiation-induced hemopoietic alterations.

MATERIALS AND METHODS

Subjects

Male Crl:CFW (SW) BR VAF/Plus Swiss-Webster mice, aged 4 months, were obtained from Charles River Breeding Labs (Raleigh, NC), and served as subjects. All animals were quarantined on arrival, and a random sample of mice were screened for evidence of disease by histopathology and serology. Mice were housed individually in polycarbonate isolator cages on hardwood chip contact bedding in an AAALAC-accredited facility under a reversed 12:12 hr light-dark cycle with lights off at 0700. Temperature was maintained at $21^{\circ} \pm 1^{\circ}\text{C}$ with $50\% \pm 10\%$ relative humidity. Commercial laboratory rodent chow (Lab Blox, Wayne, OH) and acidified (pH 2.5 using HCl) water²² were freely available.

Radiation Procedure

The mice were placed in ventilated lucite restraint devices for approximately 20 min during irradiation or sham irradiation. Animals were exposed to 10 Gy of 18.5 MeV electrons from a linear accelerator that provided 4 microsecond pulses (15 pulses/sec). Sham-irradiated animals were placed in the radiation chamber for an equivalent amount of time, but were not exposed to the electrons.

Experiment 1 -Resident-Intruder Test

Social behavior was measured using a resident-intruder paradigm, in which a resident mouse attacks an intruder that has entered its territory²⁶. This paradigm has been used widely to measure offensive aggressive behavior (observed in the resident as it attacks the intruder) and defensive behavior (observed in the intruder as it defends itself) and has ethological validity because dominant mice defend their territories in the wild^{1,2}.

The animals were housed individually for 6 weeks before irradiation because this has been reported to be an effective noninvasive method for inducing offensive aggressive behavior in mice^{6,8,19,24}. After 5 weeks of isolation, each animal was brought to the test room and paired with another weight-matched mouse for 5 to 10 min. Subsequently, the animal that dominated in this encounter was designated as the resident and the subordinate mouse became the intruder. Mice remained in the same resident-intruder pairs throughout the study, and all further testing was conducted in the resident's home cage.

On each test day, the mice were habituated to the testing room for 1 hr prior to the aggression test. The intruder was placed in the resident mouse's home cage (25.7 cm × 15.2 cm × 12.1 cm) for 5 min during the dark portion of the light-dark cycle, and the ensuing behavioral interactions were videotaped under infrared light. The following behaviors displayed by the resident mice were analyzed: number of bites, number of lunges and chases, and attack latency^{1,2,26}. Bites did not draw blood or leave any discernible mark on the intruder. Behaviors displayed by the intruder mice that were analyzed consisted of number of escapes, number of squeaks, and number of defensive upright postures^{1,2,7}. Videotapes were scored by an observer who was unaware of the treatment condition of the animals. Aggressive behavior was measured 2 days before irradiation (baseline); 1 to 3 hr postirradiation (PR); and 1, 2, 5 (N=8), 7 (N=7), 9 (N=5), and 12 days (N=3) PR in irradiated and sham-irradiated animals (N=9 on all days). Animals were weighed on each day at the conclusion of testing.

Experiment 2 -Locomotor Activity

In a separate study, a Digiscan Animal Activity Monitor (Omnitech Electronics, Columbus, OH), equipped with an array of infrared photodetectors, was used to record horizontal activity (ambulation) and vertical activity (rearing). Each animal was placed in the open field area (20.0 cm × 20.0 cm × 30.5 cm) during the dark portion of the light-dark cycle. Locomotor activity was recorded for 5 min, the time period corresponding to the length of the resident-intruder encounter in Experiment 1. Activity was monitored 2 days before irradiation (baseline); 30 min PR; and 1, 2, 5, 7 (N=16), 9 (N=12), and 12 days (N=5) PR in irradiated and sham-irradiated animals (N=16 on all days). Mice were weighed after each activity test.

Experiment 3 -Hemopoietic Parameters

Additional groups of irradiated (10 Gy) and sham-irradiated mice were used in these experiments (N=9/group/day). The mice were anesthetized by methoxyflurane inhalation and exsanguinated by cardiac puncture. Blood was collected in tubes containing EDTA. The animals were euthanized by cervical dislocation. Hemopoietic parameters (number of leukocytes, platelets, and erythrocytes, the hematocrit, and hemoglobin) were determined by a Baker Instruments System

9000 Automated Cell Counter (Allentown, PA). Blood samples were obtained 2 days before irradiation; 4 hr PR; and 1, 2, 5, 7, and 9 days PR. To control for the possible effect of repeated fighting on hemopoiesis, the mice were paired in their home cages with intruders for 5 min, on every day that the subjects in Experiment 1 were tested, and 4 hr before removal of blood.

Statistical Analysis

Behavioral data from Experiment 1 were nonparametric, and were analyzed by Mann-Whitney U tests (irradiated vs. sham animals on each test day). Activity data and body weight were analyzed

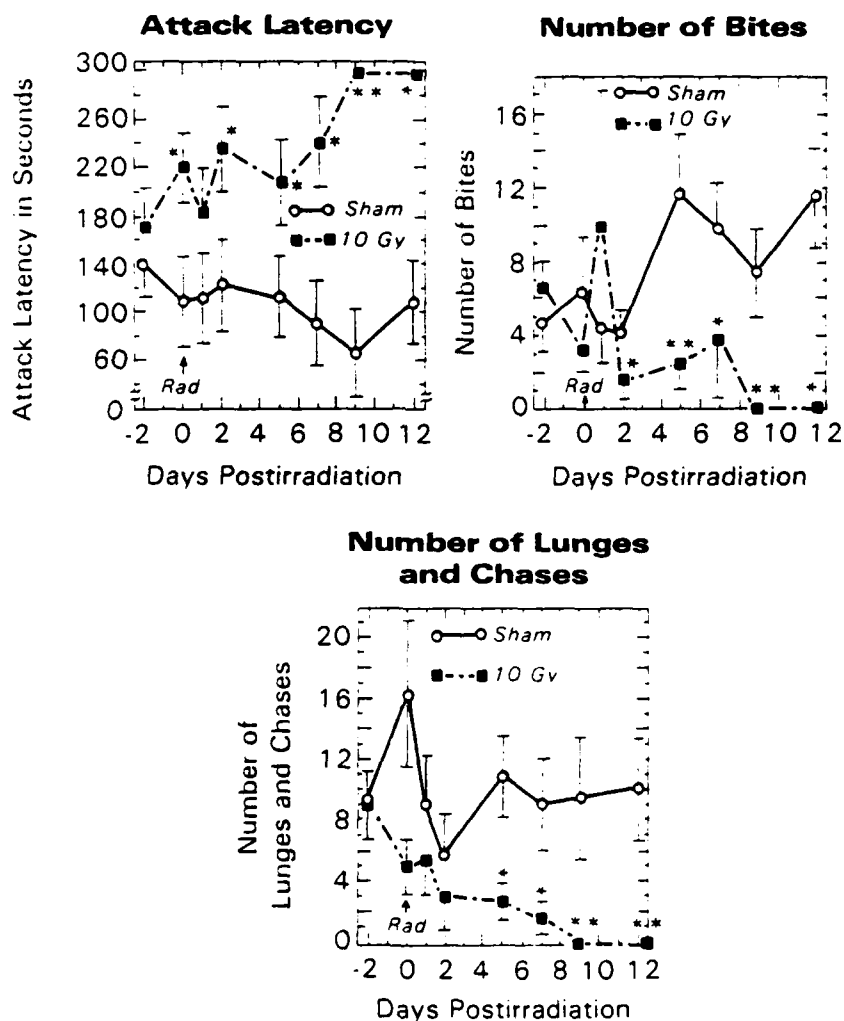


Fig. 1. Effects of 10 Gy electron radiation or sham-irradiation on aggressive offensive behaviors displayed by resident mice. Intruder mice were placed into the residents' home cages for 5 min and social behavior was videotaped 2 days before irradiation, immediately after irradiation, and 1, 2, 5, 7, 9, and 12 days postirradiation. Data are presented as means and S.E.M. (* $p < 0.05$, ** $p < 0.01$).

by t-tests (irradiated vs. sham animals on each test day). Hemopoietic data from Experiment 3 were analyzed by a one-way analysis of variance (radiation was the between groups factor). A one-tailed alpha level of 0.05 was chosen, based upon the results of previous studies^{9,14,18,20,21} and was used to evaluate all statistics.

RESULTS

Experiment 1- Aggressive Behavior

Attack latency of irradiated resident mice was significantly greater than that of sham-irradiated

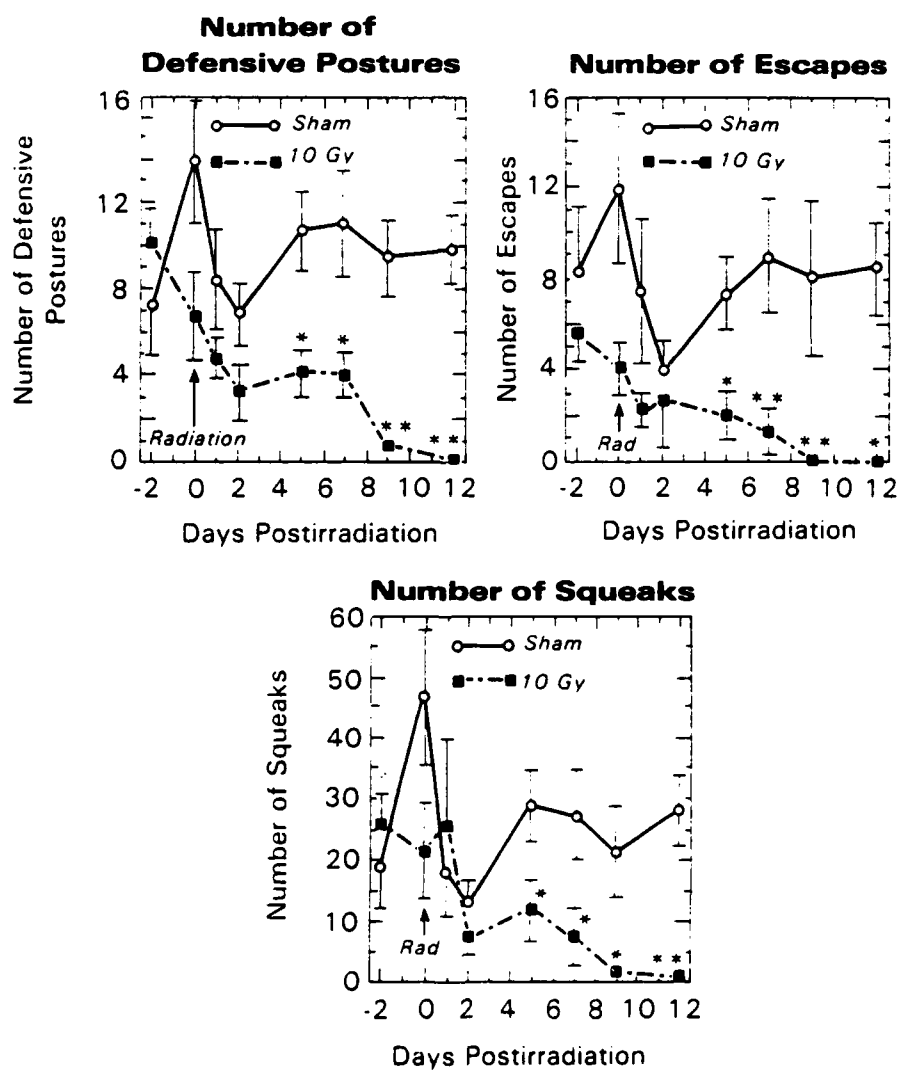


Fig. 2. Defensive behaviors exhibited by nonirradiated intruder mice placed into residents' home cages for 5 min. See Fig. 1 for additional details.

residents on day 0 PR (1 to 3 hr PR) and on days 2, 5, 7, 9, and 12 PR ($p < 0.05$) (Fig. 1). The number of bites exhibited by resident mice was significantly lower in irradiated animals than in sham-irradiated residents on days 2, 5, 7, 9, and 12 PR ($p < 0.05$) (Fig. 1). The number of lunges and chases displayed was significantly lower in irradiated residents than in their controls on days 5, 7, 9, and 12 PR ($p < 0.05$) (Fig. 1). In untreated intruders paired with irradiated resident mice, the number of defensive upright postures, escapes, and squeaks, was significantly lower than in intruders paired with sham-irradiated resident mice on days 5, 7, 9, and 12 PR ($p < 0.05$) (Fig. 2). Body weight of the irradiated mice was significantly decreased from day 5 PR ($p < 0.05$) (Fig. 4A).

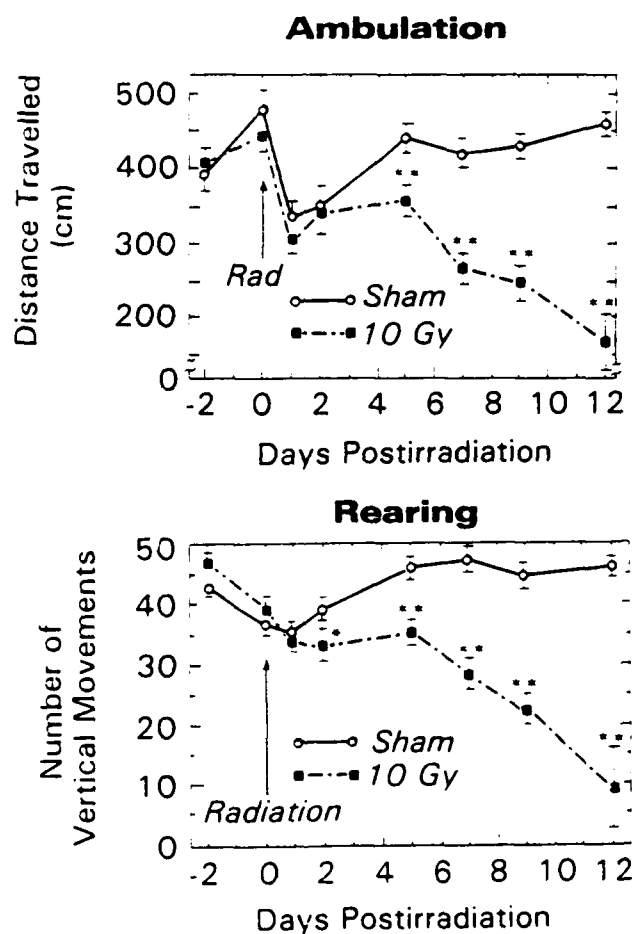


Fig. 3. Locomotor activity in mice as a function of 10 Gy electron radiation or sham-irradiation. Animals were monitored for 5 min for ambulation (horizontal activity) and rearing (vertical activity) 2 days before irradiation, immediately after irradiation, and 1, 2, 5, 7, 9, and 12 days postirradiation. Data are presented as means and S.E.M. (* $p < 0.05$, ** $p < 0.01$).

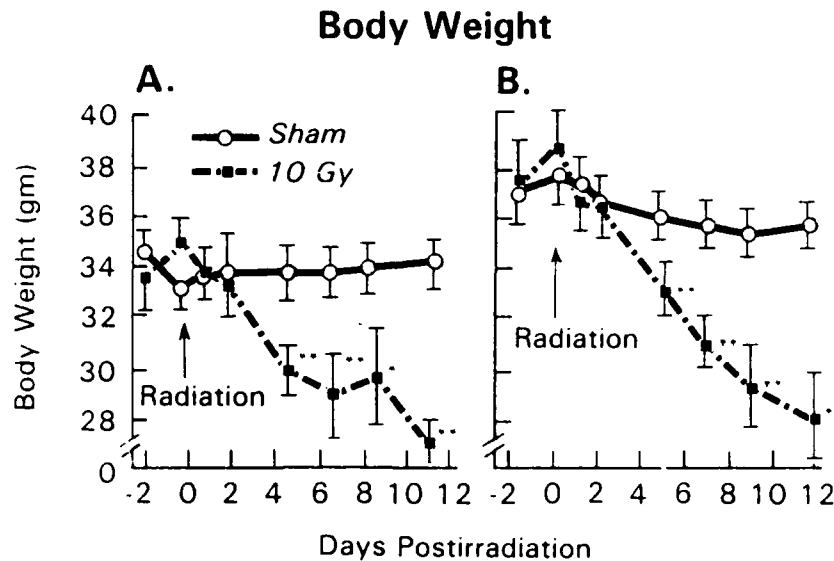


Fig. 4. Body weight in mice as a function of 10 Gy electron radiation or sham-irradiation. Animals were weighed at 2 days before irradiation, on the day of irradiation, and 1, 2, 5, 7, 9, and 12 days postirradiation. A) Resident mice from Exp. 1 (aggressive behavior). B) Mice from Exp. 2 (locomotor activity). Data are presented as means and S.E.M. (* $p < 0.05$, ** $p < 0.01$).

Experiment 2- Locomotor Activity

Rearing was significantly decreased in irradiated mice when compared with their sham-irradiated controls on days 2, 5, 7, 9, and 12 PR ($p < 0.05$) (Fig. 3). Ambulation was significantly lower in irradiated mice than in sham-irradiated animals on days 5, 7, 9, and 12 PR ($p < 0.05$) (Fig. 3). Electron radiation-induced deficits in rearing appeared earlier postirradiation than deficits in ambulation. Body weight of the irradiated animals was significantly decreased from day 5 PR, replicating the effects of Experiment 1 ($p < 0.01$) (Fig. 4B).

Experiment 3- Hemopoietic Parameters

Leukocyte and erythrocyte counts and the hematocrit were decreased significantly in irradiated mice when compared with sham-irradiated mice, on days 1, 2, 5, 7, and 9 PR ($p < 0.05$) (Table 1). Platelet count and hemoglobin were decreased significantly in the irradiated mice on days 2, 5, 7, and 9 PR ($p < 0.05$) (Table 1).

DISCUSSION

Offensive aggressive behavior, displayed by resident mice towards the intruders, decreased by 2 to 5 days PR in irradiated animals, and remained suppressed through the last test on day 12 PR. In previous studies using 10 Gy gamma photons, irradiated resident mice did not show a deficit in aggressive offensive behavior until day 7 PR^{20,21}. With 10 Gy electrons, defensive

Table 1. Hematologic Parameters Over Time as a Function of Irradiation With 10 Gy LINAC Electrons

Measure	Day-2	Day 0	Day 1	Day 2	Day 5	Day 7	Day 9
RBC-RAD	7.35 ^a 0.22 ^b	7.71 0.18	7.31* 0.13	6.59* 0.22	5.99** 0.17	4.77** 0.34	3.97** 0.20
RBC-SHAM	7.35 0.22	7.42 0.13	8.05 0.19	7.41 0.29	8.07 0.18	6.51 0.13	6.66 0.24
WBC-RAD	2.89 0.40	2.50 0.22	1.36** 0.24	0.78* 0.11	0.21** 0.02	0.47** 0.09	0.23** 0.03
WBC-SHAM	2.89 0.40	2.21 0.23	4.06 0.39	3.44 0.88	3.21 0.32	2.22 0.23	3.47 0.38
PLT-RAD	1.18 0.08	1.17 0.03	1.22 0.06	1.07* 0.05	0.61** 0.04	0.06** .006	0.04** .003
PLT-SHAM	1.18 0.08	1.14 0.06	1.33 0.04	1.32 0.11	1.38 0.03	0.89 0.12	1.25 0.04
HGB-RAD	12.8 0.4	13.0 0.3	12.6 0.2	11.2* 0.4	9.7** 0.2	8.9** 0.7	8.3** 0.7
HGB-SHAM	12.8 0.4	12.7 0.2	13.3 0.3	13.0 0.5	13.1 0.3	12.8 0.3	13.8 0.3
HCT-RAD	35.8 1.1	37.5 1.0	35.6* 0.6	31.4* 1.1	28.0** 0.7	25.4** 1.7	21.3** 1.5
HCT-SHAM	35.8 1.1	36.0 0.7	38.6 1.0	35.9 1.3	39.0 0.9	36.8 1.2	38.6 0.8

a Mean

b SEM

* $p < 0.05$ compared to sham controls** $p < 0.005$ compared to sham controlsRBC (erythrocytes) count as 1×10^6 cells/mlWBC (leukocytes) count as 1×10^6 cells/mlPLT (platelets) count as 1×10^6 cells/ml

HGB (hemoglobin) in g/dl of whole blood

HCT (hematocrit) as percent of volume

behavior in untreated intruder mice decreased in animals paired with irradiated residents by 5 days PR, and remained suppressed for the duration of the experiment. Decreases in defensive behavior may have appeared later than alterations in offensive behavior because the intruder mouse reflexively assumes defensive postures as soon as it is placed in the resident's cage and may require additional time to learn that its opponent is no longer a threat. In other studies using 10 Gy gamma photons, defensive behavior did not decrease until day 7 PR^{20,21}. These data suggest that electron radiation may produce an earlier decrement in aggressive behavior in mice than gamma photons.

Rearing in mice irradiated with 10 Gy electrons decreased significantly by 2 days PR, while ambulation decreased by 5 days PR. In studies with 10 Gy gamma photons, rearing was decreased by 5 to 7 days PR while ambulation was decreased 2 to 5 days PR^{20,21}. Thus, for the rearing measure of locomotor behavior, electron radiation appeared to produce an earlier behavioral decrement than gamma photons.

Hemopoietic parameters exhibited significant decreases after irradiation with 10 Gy electrons beginning 1 to 2 days PR, and continuing through 9 days PR (the last day blood was drawn). Mortality within this period generally results from hemopoietic injury leading to hemorrhage and infection^{9,14}. The onset and progressive severity of this hemopoietic syndrome following irradiation appears to precede the behavioral deficits observed in the animals. Several important physiological consequences of radiation injury that might influence the ability of the animals to respond normally to social stimuli include a progressive anemia, hemorrhaging, decreased food intake and corresponding weight loss, and alterations in water and electrolyte balance^{9,14}. Radiation-induced decreases in body weight appeared by 5 days PR, and reflect the presence of physiological symptoms severe enough to prevent the animal from maintaining its body weight. The decrease in aggressive behavior and locomotor activity following irradiation is more likely related to the onset of the hemopoietic syndrome rather than to direct effects of radiation on the nervous system.

The earlier onset of deficits in aggressive behavior and rearing observed after high-energy electron radiation parallels the more severe effects of this quality of radiation on avoidance responding as reported previously^{3-5,15}. Many factors are involved in this effect, including accuracy of dose measurement, dose distribution in the animal, dose rate, pulse timing, linear energy transfer (LET), and energy levels of the radiation field⁵. For many behavioral measures, radiation qualities with low LET (gamma photons, electrons, bremsstrahlung) are often more disruptive than those with high LET (neutrons)⁵, although high LET radiation generally has a more rapid effect on mortality^{5,30,31}. For example, in shock-avoidance tasks in both pigs and monkeys, irradiation with gamma photons had a more disruptive effect than neutrons^{13,28}. Moreover, bremsstrahlung radiation produced greater behavioral incapacitation in monkeys on a shock-avoidance visual-discrimination task than neutrons³⁰. In contrast, the intensity of conditioned taste aversions, a model for radiation-induced emesis, has been found to be positively correlated with LET²⁵. Similarly, neutron radiation produced a greater frequency of vomiting in monkeys than exposure to gamma photons^{23,31}. In addition, mixed radiation (60% gamma and 40% neutron), delivered in a pulse, suppressed performance of a shock-avoidance lever-press task in monkeys more than X-rays²⁷.

In the present studies, electron radiation was found to exert a suppressive effect on aggressive behavior, locomotor activity, body weight, and hemopoiesis. High-energy electrons appeared to produce behavioral decrements earlier postirradiation than gamma photons^{20,21}. Both radiation quality and type of behavioral task are important factors in evaluating the nature of radiation-induced behavioral deficit, and should be considered when extrapolating dose-response effects.

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